A Program for Neuropsychological Investigation of Deep Brain Stimulation (PNIDBS) in Movement Disorder Patients: Development, Feasibility, and Preliminary Data

*†Chris E. Morrison, M.Phil., *†Joan C. Borod, Ph.D., *Mitchell F. Brin, M.D., ‡Sarah A. Raskin, Ph.D., §Isabelle M. Germano, M.D., §Donald J. Weisz, Ph.D., and *C. Warren Olanow, M.D.

Departments of *Neurology and §Neurosurgery, Mount Sinai School of Medicine, New York, New York; †Department of Psychology, Queens College and The Graduate Center of the City University of New York, New York; and ‡Department of Psychology, Trinity College, Hartford, Connecticut

Objective: This technical report and feasibility study propose a standardized method for collecting neuropsychological data in patients undergoing the deep brain stimulation (DBS) procedure. Background: Programs for standardizing motor data collected in studies investigating surgical therapies for Parkinson disease are already widely used (e.g., Core Assessment Program for Intracerebral Transplantations). The development and rationale for the proposed Program for Neuropsychological Investigation of Deep Brain Stimulation (PNIDBS) are outlined, and support for the feasibility of these methodologies is provided via preliminary data. Method: The PNIDBS includes a core battery of neuropsychological tests that assesses a wide range of cognitive functions (attention, language, visuospatial, memory, and executive) as well as depression. Using the PNIDBS, three Parkinson disease and two dystonia patients were evaluated at baseline and after surgery, once with stimulation off and once with stimulation on. Results: Patients with severe motor disabilities were able to complete the PNIDBS. These preliminary data suggest that the DBS procedure as a whole had a minimal impact on cognitive functioning in most patients studied. There was also some evidence that the one patient who showed cognitive decline after the DBS procedure had demographic and clinical characteristics that may have put him at risk for this decline. Conclusions: The procedures in the PNIDBS were systematically developed and are feasible to execute. The relatively brief core battery has multiple versions and can be supplemented to meet individual investigator needs. By evaluating the components of the DBS procedure (electrode placement and stimulation), the PNIDBS can address clinical questions regarding the cognitive effects of the DBS procedure as well as investigate basic scientific issues regarding how different cognitive functions are affected when subcortical-prefrontal circuits are manipulated by the DBS procedure. NNBN 2000;13:204–219

Chronic high-frequency deep brain stimulation (DBS) in select nuclei is one of the newer surgical procedures for relief of severe movement disorder symptoms. Examination of neuropsychological functioning after stereotactic placement of indwelling electrodes and chronic high-frequency stimulation is in the preliminary stages, and many institutions are now initiating programs to study the motor, cognitive, and affective ramifications of these procedures. A brief overview of the DBS procedure and a more comprehensive description of important methodological concerns when studying cognition and the DBS procedure (both electrode implantation and high-frequency stimulation) are provided as a background for presentation of a proposed Program for Neuropsychological Investigation of Deep Brain Stimulation (PNIDBS). The theoretical and practical reasoning used during the development of this proposed standardized method of neuropsychological investigation are outlined to support our proposition that the PNIDBS is an empirically sound method for studying cognitive change associated with the
two aspects of the DBS procedure (i.e., surgery and stimulation). Finally, this technical report and feasibility study present preliminary data from a small sample of patients with either PD or dystonia. With these data, we demonstrate how the PNIDBS is used and that the methodologies described in the proposed program are feasible to execute.

Deep Brain Stimulation

It was observed during neurosurgical lesioning procedures in PD patients that high-frequency stimulation in specific neural areas had an effect on motor symptoms similar to that of a surgically produced lesion (1). Because stereotactic lesions had been observed to successfully treat PD symptoms, particularly tremor, it was proposed that instead of a destructive lesion, high-frequency stimulation could be applied with permanently implanted electrodes to reduce the severity of motor symptoms (2). This procedure for inducing a “functional” lesion attempts to achieve neuroanatomic (disruption of abnormal activity) and functional (reduction of motor symptoms) outcomes similar to those of a surgical lesion (3).

The DBS procedure involves two phases: (1) stereotactic placement of stimulating electrodes and surgical internalization of the pulse generator, and (2) initiation of chronic high-frequency DBS. Some of the risks of surgery for lead and generator implantation may include but are not limited to hemorrhage, permanent or transient neurologic deficits, infection, seizures, mechanical or electric problems with the equipment, and migration of the stimulating electrode (4–7). A recent review of the literature (8) found the frequency of surgical and mechanical type adverse events per study to range from 0 to 12%. In the second phase of the procedure, the stimulator is turned on and the process of making stimulation parameter adjustments, in order to determine clinically optimal settings, begins. Potential risks during stimulation may include paresthesias, dystartria, disequilibrium, temporary worsening of motor symptoms, and visual changes (6,7,9–11). The frequency of stimulation-related adverse events is much higher than that for the surgical procedure itself (up to 46.5%); however, these side effects are nearly always reversible when stimulation is adjusted or turned off (8).

The potential benefits of the DBS procedure are the reduction or elimination of medically refractory motor symptoms and the flexibility of the procedure itself (i.e., its reversibility and modifiability). Thus far, DBS has been used to treat motor symptoms in PD and essential tremor (ET). PD is a progressive degenerative akinetic movement disorder characterized by tremor, rigidity, bradykinesia/akinesia, and/or postural instability (12). This disease results primarily from a loss of dopaminergic cells in the substantia nigra (13). In ET, the typical motor character-
might be especially true for those patients who have some level of preexisting cognitive impairment. Second, cognitive change may result from chronic DBS itself. If it is determined that there is improvement or lack of further decline in cognitive functioning associated with chronic DBS, the known benefits of this procedure are increased. If, however, cognitive decline is noted in either generalized or in specific areas, patients and their physicians should take this information under serious consideration when deciding whether DBS is the appropriate treatment option.

From a basic research perspective, the DBS procedure presents several unique opportunities for studying neuroanatomic substrates of cognitive functioning. It allows for extensive neuropsychological investigation of cognition before and after a largely reversible direct brain manipulation in human subjects. Similar opportunities are found during brain mapping procedures or during the intracarotid amobarbital sodium (Wada) procedure. However, during these procedures, tests of cognitive functioning are limited to durations of seconds or minutes. In the case of DBS, where stimulation can be turned on or off for any interval and the stimulation parameters can be manipulated, a much more detailed assessment of higher cognitive functions in multiple cognitive domains can be obtained after neurophysiologic modification of neural systems.

As a result of the different methodologies and research designs used, there is a great deal of variability in the data reported in some areas of neuropsychological research, making firm conclusions difficult to draw. Because the number of patients undergoing the DBS procedure at any one site may be limited, it is important to obtain the most information possible from each subject regardless of which institution performed the testing. To this end, we outline here a proposed standard program for neuropsychological study of movement disorder patients who receive this surgical treatment. Generalized use of similar methodologies and tests would not only increase the comparability of data collected across studies, therefore maximizing the information obtained from each patient, but would also increase the reliability and validity of those findings. A similar approach has been employed in studying the motor effects of neurosurgical treatments for PD. The Core Assessment Program for Intracerebral Transplantations (CAPIT) (34) was developed to standardize the diagnosis and evaluation of patients with PD undergoing fetal tissue transplantation so that data collected from multiple centers could be directly compared. Subsequently, the CAPIT has been used in studies evaluating a range of other neurosurgical treatments for PD (35-37), demonstrating how a standardized approach can be used to increase comparability of data across institutions and treatments. For similar reasons, it seems prudent and worthwhile to adopt a standardized approach for studying the cognitive effects of the DBS procedure, at least in the early phases of research in this area.

Toward this goal, the discussion below includes important methodological considerations when studying cognition in patients with movement disorders who are undergoing the DBS procedure. Also discussed is the rationale for the development of a core neuropsychological test battery designed for use in this patient population. Combining clinically and empirically important neuropsychological tests and experimental procedures as well as issues of feasibility, we have developed the PNIDBS.

**Methodological Considerations When Studying the Cognitive Effects of DBS in Movement Disorder Patients**

**Physical Limitations and Assessment**

Surgical candidates are generally moderately to severely disabled by their movement disorder and do not receive sufficient clinical benefit from medical treatments. Therefore, many patients are likely to have significant difficulty in manipulating objects or performing writing or drawing tasks of any kind. Furthermore, marked dyskinesia, bradykinesia, tremor, or dystonic movements may have an impact on a patient's residual ability to quickly perform cognitive tasks with a motor component. Finally, when the dynamic abnormal movements involve the torso and head, a patient's ability to perceive complex visual stimuli may be compromised. These limitations and possible confounds need to be addressed when neuropsychological tests are selected.

**Movement Disorder Pharmacotherapies and Cognition**

There is an ongoing debate in the literature as to whether levodopa has an effect on cognition, and if so, what that effect might be. Some researchers claim that although there are marked improvements in motor functioning, there are no cognitive changes as a result of levodopa or dopamine agonist treatment (38,39). This contrasts with the findings of investigators who report nonspecific arousal effects of levodopa (40,41), which may generally improve cognitive functioning as a result of increased attentional abilities. Still others report mixed results, with some cognitive domains being influenced positively or negatively, although others are not affected by levodopa therapy (42-45). Much less is known about the cognitive effects of dopamine agonists; however, in neurologically normal individuals, they have been found to impair select cognitive domains (46,47).

Other common pharmacotherapies used to treat movement disorders include anticholinergics, benzodiazepines, monoamine oxidase inhibitors, catechol-O-methyltrans-
ferase inhibitors, dopamine antagonists, gamma-aminobutyric acid agonists, and local injections of botulimum toxin (48–50). Some of these medications can affect cognitive functioning. Anticholinergic medications have been found to impair memory and sometimes executive functions (51–55). Benzodiazepines may sedate patients (56), resulting in reduced cognitive performance. When the monoamine oxidase inhibitor selegiline has been examined, some studies indicate that there are no cognitive changes after treatment with this medication (57,58), although others find cognitive improvement with treatment in nondemented individuals (59). The results of preliminary studies that have included cognitively normal subjects suggest that catechol-O-methyltransferase inhibitors selectively enhance cognitive performance (60).

After DBS implantation, medication dosages may be adjusted depending on the degree of symptomatic benefit. In an effort to control for drug-related cognitive changes, the ideal situation would call for patients to undergo neuropsychological testing in all experimental conditions (i.e., baseline, stimulation-off, stimulation-on) after withdrawal of drugs that can have cognitive effects. For example, the period of drug withdrawal commonly used in studies that assess the cognitive effects of levodopa is approximately 15 hours (e.g., 42,43). However, many movement disorder medications cannot be safely discontinued via abrupt withdrawal in the way that levodopa can (e.g., benzodiazepines, anticholinergics). Furthermore, some patients may not be able to tolerate any period of drug withdrawal. Therefore, to evaluate the cognitive effects of DBS, if it is not possible to test patients in the ideal “drug-free” state, at the minimum, dosages of medications with cognitive effects should remain constant across testing conditions.

When Testing Should Take Place

To evaluate any cognitive changes that may be associated with the individual components of this procedure, at least three testing conditions are important to include: presurgical baseline, postsurgical stimulation-off, and postsurgical stimulation-on. A comparison of baseline scores with those obtained in the stimulation-off condition yields information about the cognitive effects of the procedure for electrode placement, and a comparison of stimulation-off versus stimulation-on conditions allows for independent examination of the cognitive effects of high-frequency stimulation. The overall effect of the procedure on cognition can be evaluated by comparing the baseline scores with those of the stimulation-on condition.

If patients are able to tolerate medication withdrawal, there are four theoretically possible postsurgical testing conditions: off-drug/stimulation-off, off-drug/stimulation-on, on-drug/stimulation-off, and on-drug/stimulation-on. For these four postsurgical conditions to be comparable, they would need to take place within a relatively short period of time. There is one report of a patient who was administered a short series of neuropsychological tests in all four of these conditions (the two on-drug conditions separated from the two off-drug conditions by 3 weeks) (67). The PNIDBS does not include four conditions per

Which Conditions To Test In

To date, a limited number of controlled neuropsychological studies investigating the cognitive effects of the DBS procedure have been conducted. Caparros-Lefebvre et al (61), Troster et al (62,63), and Ardouin et al (64) assessed patients before surgery and after surgery with stimulation on. This experimental design, although providing important clinical information, does not examine the full range of potential effects that the individual aspects of the procedure may have. In fact, Caparros-Lefebvre et al (61) comment that the variability in their data may have been the result of surgical factors rather than DBS. Because a postsurgical stimulation-off condition was not included in their study, the effects of surgery versus DBS could not be differentiated. In contrast, some authors (65,66) have evaluated just the effects of stimulation by comparing cognitive performance while the stimulator was either on or off.

To evaluate any cognitive changes that may be associated with the individual components of this procedure, at least three testing conditions are important to include: presurgical baseline, postsurgical stimulation-off, and postsurgical stimulation-on. A comparison of baseline scores with those obtained in the stimulation-off condition yields information about the cognitive effects of the procedure for electrode placement, and a comparison of stimulation-off versus stimulation-on conditions allows for independent examination of the cognitive effects of high-frequency stimulation. The overall effect of the procedure on cognition can be evaluated by comparing the baseline scores with those of the stimulation-on condition.

If patients are able to tolerate medication withdrawal, there are four theoretically possible postsurgical testing conditions: off-drug/stimulation-off, off-drug/stimulation-on, on-drug/stimulation-off, and on-drug/stimulation-on. For these four postsurgical conditions to be comparable, they would need to take place within a relatively short period of time. There is one report of a patient who was administered a short series of neuropsychological tests in all four of these conditions (the two on-drug conditions separated from the two off-drug conditions by 3 weeks) (67). The PNIDBS does not include four conditions per
follow-up interval for several reasons. First, not every patient is able to tolerate a period of drug withdrawal. Second, even if every test used had four alternate forms, four complete evaluations within a short time (e.g., data for each condition collected across 2–4 weeks for the “3-month” postoperative assessment) could result in confounding practice effects. Third, patients may not be inclined to submit to this volume of testing and could decline participation altogether because of the exhaustive study requirements (e.g., four evaluations both at the 3-month follow-up interval and again at the 1-year follow-up interval); such subject attrition weakens a study. Therefore, only two postoperative conditions (optimally occurring after medication withdrawal but can also be done while patients are taking medications) for each follow-up interval are recommended and thus included in the PNIDBS. This method seems to strike a balance between investigating the cognitive effects of DBS in a thorough and well-controlled manner and reducing experimental confounds and subject attrition.

Development of a Core Neuropsychological Test Battery for Studying the DBS Procedure

Some general principles for the development of a neuropsychological battery to assess movement disorder patients undergoing the DBS procedure include the need for brevity. In our experience, the tolerance for testing in this disabled population is in the range of 1 to 2 hours. This is largely based on the limit that we have encountered with severe dystonia patients and patients with PD while off medications. Medicated moderate-to-severe PD and ET patients and moderate dystonia patients have greater test tolerance. A second consideration is test repeatability; there are at least three conditions to be studied, and perhaps more, if long-term follow-up testing is conducted. To address the issue of practice effects, where possible, tests with alternate versions were selected for inclusion in the PNIDBS. Although there is controversy over whether alternate forms completely eliminate practice effects, use of alternate forms seems to be the best method available at this time for reducing this problem (68). Third, because cognitive change after DBS has not yet been fully studied, it is not known if change might occur in isolated cognitive areas or across a range of intellectual abilities. To explore this, a battery should include tests assessing multiple cognitive domains.

Of the three movement disorders thus far treated with DBS (idiopathic dystonia, PD, and ET), only PD is associated with potential presurgical cognitive deficits even if patients are not demented. Therefore, in addition to our goal of developing a battery that is empirically sound, it is able to assess a variety of cognitive abilities, and can be completed by a range of movement disorder patients, the selection of tests for the core neuropsychological test battery was based, in part, on deficits observed in non-demented patients with PD. At this time, there is no information on how patients with idiopathic dystonia or ET perform on any of the selected measures.

Attention

A measure of basic attention is important to include when examining any population or procedure. The digit span test is a widely used test of immediate attention. The Repeating Numbers subtest of the Randt Memory Test (RMT) (69) has five equivalent versions to use in a repeatable battery. Scores from the forward and backward components of this test (i.e., the total number of correct numeric sequence repetitions) can be evaluated separately to study attention span apart from working memory. This is useful because patients with PD have been found to perform differently on these two aspects of the Digit Span test (70,71). Standard administration of the RMT Repeating Numbers subtest is used in the PNIDBS.

A test of more sustained attention is also warranted, particularly in light of the vigilance deficits that have been observed in patients with PD (72–74). A continuous performance test is ideal for this purpose, although such tests may require a minimum of 20 to 30 minutes to administer. The Brief Test of Attention (BTA) (75) assesses attention and concentration beyond immediate span and is relatively quick to administer. Furthermore, its two sections, which require subjects to mentally count the number of either letters (section 1) or numbers (section 2) in 10 trials of progressively longer sequences, can be used individually in different versions of a repeatable test battery. Although we have not collected data on the reliability of using the two parts as alternate forms, they are so analogous that it is likely there would be similar performance on the two sections. Standard administration and scoring of the BTA are used in the PNIDBS.

Language

Language deficits are not generally associated with PD, ET, or dystonia; however, poor performance on fluency and confrontation naming tasks has been observed in some PD studies (73,76–79). Even if baseline deficits in these areas are not present, fluency and naming deficits have been observed after thalamotomy (80,81) and pallidotomy (82,83) and would therefore be important to assess after the DBS procedure. Verbal fluency tasks can require generative naming to semantic or phonemic cues. Both types of cuing should be included because performance after surgery may differ on these two types of tasks, thus revealing subtle variations in cognitive change associated with the DBS procedure. Because the letters F, A, and S were used in our alternating fluency task (see Executive section), we have included the letter cues.
from the Multilingual Aphasia Examination (84). Only one letter per condition is used, and the standardized administration is employed (i.e., total number of words per 60 seconds) in the PNIDBS. A single letter per condition is administered not only to shorten administration time but to ensure that additional letters are available from the same measure for alternate versions of a repeatable battery.

As a result of the surgery, there may be potential changes in oral motor speed. To ensure that any changes observed on verbal fluency tasks are the result of an altered ability to quickly retrieve semantic information from memory and not just secondary to improvements in oral motor speed or agility, a control task should be included. A measure of oral motor speed that does not also require effortful memory retrieval would involve timed verbalization of automatic overlearned material. If a marked change in speed is observed in reciting automatized sequences, this information can be included in the outcome analysis; thus separating oral-motor-based changes from more language-based changes. The PNIDBS includes three automated sequence measures (i.e., number of seconds required to recite the alphabet, months of the year, numbers from 1–20). The average time to complete these three tasks is used as the outcome variable.

With regard to confrontation naming, the Boston Naming Test (BNT) (85) is the most widely used test of this function. Mack et al (86) published four 15-item versions derived from this 60-item task. The 15-item versions are highly correlated with the full-length BNT and can be used in multiple versions of a repeatable battery. Standard administration and scoring (87) of this measure are used in the PNIDBS. Some authors characterize naming ability and verbal fluency as “frontal” or executive functions. Regardless of how these functions are conceptualized, for the reasons discussed previously, they are important to assess in patients undergoing the DBS procedure.

Visuospatial

Because it is not yet clear whether the DBS procedure affects visuospatial processing, it would be helpful to evaluate multiple aspects of this cognitive domain. A test of basic perception and discrimination should be administered before tests of higher order visuospatial processing for a number of reasons. First, basic perception deficits have been found in nondemented patients with PD (71, 88–90). Second, the sometimes extremely dynamic movements of the torso and/or head seen in the moderate to severe stages of various movement disorders can adversely affect primary perceptual abilities. Finally, in the case of electrode placement in the GPi, probes may pass within the optic tract during the process of identifying an appropriate implantation site, potentially causing a visual field defect and altering perceptual ability. A simple test of basic perception that does not require a motor response is the Visual Form Discrimination Test (91). This measure, with standard administration and scoring (91), is used in the PNIDBS.

To address higher order visuospatial processing, measures of personal and extrapersonal orientation are included in the PNIDBS. Some nondemented patients with PD have been found to be impaired in these areas (88,92–97). The Judgment of Line Orientation Test (JLOT) (91) and the Standardized Test of Direction Sense (98) are easily administered tests of these functions that do not require a motor response. The JLOT can be divided into two versions by separating the odd and even items (99), thus reducing administration time and creating two separate versions for a repeatable test battery. Standard administration and scoring (91,98) of these measures are used in the PNIDBS. Another commonly used test of complex visuospatial ability is the Hooper Visual Organization Test (100). This particular test, however, while an excellent clinical measure, does not lend itself to repeatability. Subjects may remember their previous response from partial stimulus information and not actually perform the mental rotation necessary to obtain the answer on each administration.

Memory

As noted, because these populations often have severe motor disabilities, there are no writing requirements in the core neuropsychological test battery; therefore, recall of visual material is not assessed. To assess visual recognition memory, the RMT (69) contains a subtest requiring recognition of line drawings of common objects. We include this subtest in the PNIDBS because it has an immediate and delayed component as well as five equivalent versions. (The recognition form of the Benton Visual Retention Test [101] can also be used because it has several versions. Only immediate recognition or recognition after a 15-second delay is possible with this test, however.) Although we administer this task per the instructions provided in the test manual, we do not collect the verbal recall or 24-hour delay trials. To obtain the most information possible when scoring this measure, we count the total number of correct responses in 15 trials in both the immediate and 5-minute delay conditions rather than just indicating if a “yes” response was given to the seven target items.

More flexibility is possible in the domain of verbal memory. In PD, nondemented patients have been found to learn at slower rates, use less effective learning strategies, and recall less than matched control subjects (89,102–105). Verbal recognition memory can also be affected in PD (89,105,106), although this is less often the case. The California Verbal Learning Test (CVLT) (107) can assess learning across several trials, proactive and retroactive in-
terference, delayed recall, and delayed verbal recognition conditions, as well as the use of efficient versus inefficient learning strategies and the ability to facilitate recall with cuing. In light of the verbal memory deficits observed in PD, particularly those related to difficulty with spontaneous use of implicitly presented learning strategies, the CVLT can provide the most information within a given test. There are only two versions of the CVLT; however, The Hopkins Verbal Learning Test (HVLT) (108) can assess learning across several trials, use of efficient learning strategies, and verbal recognition memory, but most importantly, it has six alternate equivalent versions. The standard administration of the HVLT, however, only requires three learning trials and one delayed recognition trial compared with the five learning trials, immediate and delayed cued recall trials, and delayed recognition trial of the CVLT.

To take advantage of the six equivalent versions, we modified the administration of the HVLT. Two learning trials, for a total of five, as well as a delayed recall trial and immediate and delayed cued recall trials were added. (Recently, a revised version of the HVLT was published, which includes a delayed recall trial [109]. Because the current study began 2 years before the publication of the revised HVLT, we continue to use our own modification of the HVLT. However, because there are validity and reliability data available for the revised HVLT, that version may be more appropriate for future studies.) Our modifications allow for a more detailed characterization of learning and memory functioning. We believe that this was important because of the slowed learning and retrieval deficits observed in PD. This modified administration makes the HVLT more similar to other clinically used list-learning tasks. We included six scores from this task, the number of words recalled after five learning trials, the number of words recalled in the immediate cued recall trial, the number of words recalled after a 30-minute delay, the number of words recalled in the delayed cued recall trial, the number of semantic clusters across the five learning trials (included as an executive function measure), and the total number of correct responses (hits and correct rejections) on the delayed recognition trial. The Rey Auditory Verbal Learning Test (110) is another commonly used list-learning task with several versions; however, the words in this measure cannot be grouped in semantic categories.

Memory for verbal material presented in a contextual format, such as a short story, is also important to assess because this format for learning is generally more similar to that which takes place outside the laboratory (110), lending ecologic validity to this method of learning. The short stories of the Logical Memory subtest of the Wechsler Memory Scale–Revised (111) are widely used in clinical and research testing; however, there are only two equivalent stories to be used in an experimental design that optimally requires three if not more testing conditions. The RMT contains five equivalent short stories that can be used to assess verbal memory for material presented in this format. The PNIDBS uses the standard administration and scoring of this measure (69).

Executive

The assessment of executive functioning in the proposed core battery is limited to aspects of cognitive set for the following reasons. First, it has been observed that many patients with diseases of the basal ganglia, particularly PD, have difficulties with this aspect of executive functioning (77,112-116). Therefore, because the procedure under study involves manipulation of subcortical structures, and because there is direct and indirect evidence that the population of patients undergoing the DBS procedure has subcortical neuropathology, we decided to focus on this aspect of executive functioning. Second, there is a wide range of executive type functions, and given the general guidelines that we used in developing the battery, in particular brevity, we could not cast our assessment net too widely in this cognitive domain. Finally, although there are available measures of many different types of executive deficits, few of these measures are repeatable or have alternate versions, further limiting our scope of investigating executive functions.

Parkinson disease patients have been described as having both a decreased "shifting aptitude" (77,112), which involves difficulty in altering response patterns from one to another set of response options, and an instability in their response set (112,117), which is identified as difficulty in maintaining a pattern of responding when multiple response options are available. A widely used task that assesses these abilities is the Wisconsin Card Sorting Test (WCST) (118). Although some studies find that patients with PD perform poorly on this measure (87,114,119-121), Flowers and Robertson (117) have indicated several reasons why the WCST may not be the best test to use in the PD population. One of their concerns is based on evidence that normal geriatric subjects could rarely progress beyond the first sorting category (118). Therefore, these authors (117) developed the Odd Man Out Test (OMOT), which assesses various aspects of cognitive set but does not have the limitations for use in the PD population that the WCST does. Administration time required for the OMOT is less than that required for the WCST, and the test has been useful in detecting impairment in patients with PD (117,122,123). Furthermore, the OMOT has been able to index impairment even after repeated administration (117), suggesting that it has limited practice effects and would be appropriate for use in a repeatable test battery. We administer this task per the instruc-

Neuropsychiatry, Neuropsychology, and Behavioral Neurology
somatic symptoms that are not the result of depression in elderly patients, questionnaires include many items related to somatic symptoms. The Geriatric Depression Scale (GDS) is a measure sensitive to these issues; it was designed for use in geriatric populations and is less likely to yield inflated scores than some other self-report depression inventories. Standard administration and scoring of this measure are used in the PNIDBS.

**Summary**

Based on the rationale described here, we developed a core neuropsychological test battery for use in studying cognitive functioning in movement disorder patients undergoing the DBS procedure. The battery includes 22 measures and assesses attention, language, visuospatial, memory, and executive functions (Table 1). The battery also includes a depression measure. The entire battery requires approximately 1 hour to administer. It was derived, in part, from a longer test battery developed to assess the general population of patients with PD (134).

The purpose of the current preliminary investigation was to test the feasibility of the PNIDBS. This was accomplished by administering the core neuropsychological test battery to a small number of movement disorder patients in several testing conditions in accordance with the methodologies described in the PNIDBS.

**METHOD**

**Procedures**

Three patients with idiopathic PD and two with idiopathic dystonia were included after giving written informed consent. Baseline "off" Hoehn and Yahr (135) scores for the patients with PD were as follows: PD Patient 1 (PD1) = 3, PD Patient 2 (PD2) = 5, and PD Patient 3 (PD3) = 3, Baseline Burke, Fahn, Marsden Scale subscale scores (136) for the dystonia patients were as follows: dystonia Patient 1 (Dy1) = 11 and dystonia Patient 2 (Dy2) = 51. None of the subjects were demented as determined by performance within the normal range on the Dementia Rating Scale (137), and estimated IQ was in the average range as measured by the National Adult Reading Test–Revised (138). Individual demographic and clinical characteristics are presented in Table 2. In patients with PD, the Dementia Rating Scale and National Adult Reading Test–Revised were given while the patients were receiving medication. During the three experimental conditions, patients with PD were tested after a 10-hour to 12-hour period of antiparkinsonian medication withdrawal. Dystonia patients were not tested after a period of medication withdrawal because Dy2 could not be taken off her clonazepam and Dy1 was not taking any medications. Patients were administered the core PNIDBS neuropsychological test battery described previously within 1 month (mean = 14 days, SD = 16.8) before surgery. All subjects received unilateral electrode placement (see Table 2 for implantation side and number of recording/stimulating electrode passes); place-
ment was in the STN in patients with PD and in the posteroverentral GPi in dystonia patients. Postoperative magnetic resonance imaging scans verified that the stimulating electrodes were located in the target nuclei. A minimum of 1 month after surgery (mean = 31 days, SD = 4.7), two alternate equivalent versions of the test battery given on the presurgical day were administered 1 day apart. One version of the battery was given while the patient’s stimulator was off, and a third version was given while the stimulator was turned on (after stimulation parameters had been adjusted for maximum clinical benefit). Testing took place a minimum of 12 hours after a change in stimulator status. The order of the alternate forms of the test battery was counterbalanced across subjects as was the order of the postsurgical conditions (stimulator on or off first). The neuropsychological test battery was as described previously. Specific letters used in the phonemic verbal fluency task were C, L, and P, with one letter per condition. On the semantic verbal fluency task, the categories were foods, kitchen items, and occupations, with one category per condition. On the alternating fluency task, subjects were first asked to generate words beginning with the letter F for 60 seconds; during the next 60-second test interval, they were asked to generate words beginning with the letters A and S in alternation. The total number of words beginning with the letters A and S was subtracted from the total number of words beginning with the letter F (128).

### TABLE 1. Neuropsychological test battery from the Program for Neuropsychological Investigation of Deep Brain Stimulation and patient data from the Procedure comparison

<table>
<thead>
<tr>
<th>Test</th>
<th>Reference</th>
<th>Individual measure †</th>
<th>Time ‡ (minutes)</th>
<th>Improvement</th>
<th>Decline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention</td>
<td>Randt Memory Test: Repeating Numbers</td>
<td>Randt and Brown, 1984</td>
<td>Forward score: 14</td>
<td>2</td>
<td>Dy2</td>
</tr>
<tr>
<td></td>
<td>Brief Test of Attention</td>
<td>Schretlen, 1989 (75)</td>
<td>Backward score: 14</td>
<td>2</td>
<td>PD3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total subset score: 10</td>
<td>5</td>
<td>Dy1, Dy2</td>
</tr>
<tr>
<td>Language</td>
<td>Controlled Oral Word Association</td>
<td>Benton and Hamsher, 1978 (84)</td>
<td>Letter fluency $</td>
<td>2</td>
<td>PD1, PD3, Dy1</td>
</tr>
<tr>
<td></td>
<td>Boston Diagnostic Aphasia Exam</td>
<td>Goodglass and Kaplan, 1983 (142)</td>
<td>Category fluency $</td>
<td>2</td>
<td>PD2, PD3</td>
</tr>
<tr>
<td></td>
<td>Boston Naming Test: 15 items</td>
<td>Mack et al, 1992 (86)</td>
<td>Total score: 15</td>
<td>3</td>
<td>PD1</td>
</tr>
<tr>
<td>Visuospatial</td>
<td>Visual Form Discrimination Test</td>
<td>Benton et al, 1983 (91)</td>
<td>Total score: 32</td>
<td>7</td>
<td>Dy2</td>
</tr>
<tr>
<td></td>
<td>Judgment of Line Orientation Test: 15 items</td>
<td>Woodard et al, 1996 (99)</td>
<td>Total score: 15</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Executive</td>
<td>Standardized Test of Direction Sense</td>
<td>Money, 1976 (98)</td>
<td>Total score: 32</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Odd Man Out Test</td>
<td>Richards et al, 1983 (121)</td>
<td>Total score: 40</td>
<td>7</td>
<td>PD2</td>
</tr>
<tr>
<td></td>
<td>Stroop Color and Word Test: 45-second trial</td>
<td>Stroop, 1935 (124)</td>
<td>Interference score</td>
<td>3</td>
<td>PD3, PD1, PD2</td>
</tr>
<tr>
<td></td>
<td>Alternating fluency task</td>
<td>Newcombe, 1969 (125)</td>
<td>F - A/S = Score</td>
<td>3</td>
<td>PD3, Dy1, PD1, PD2</td>
</tr>
<tr>
<td>Verbal learning</td>
<td>RMT: short story</td>
<td>Randt and Brown, 1984</td>
<td>Immediate recall: 20</td>
<td>2</td>
<td>Dy1</td>
</tr>
<tr>
<td></td>
<td>HVLT: modified</td>
<td>Brandt, 1991 (107)</td>
<td>Total recall: 60</td>
<td>6</td>
<td>PD2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Immediate cued recall: 12</td>
<td>1</td>
<td>PD2, Dy2</td>
</tr>
<tr>
<td>Delayed verbal recall</td>
<td>RMT: short story</td>
<td>Randt and Brown, 1984</td>
<td>Delayed recall: 20</td>
<td>2</td>
<td>Dy1</td>
</tr>
<tr>
<td></td>
<td>HVLT: modified</td>
<td>Brandt, 1991 (107)</td>
<td>Delayed free recall: 12</td>
<td>1</td>
<td>PD1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Delayed cued recall: 12</td>
<td>1</td>
<td>Dy2, PD1</td>
</tr>
<tr>
<td></td>
<td>RMT: Picture Recognition</td>
<td>Randt and Brown, 1984</td>
<td>Immediate recognition: 15</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Delayed recognition: 15</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

*Instances of >15% change in the stimulation-on compared with baseline condition. †Total number of points possible listed after colon. §Approximate administration time in minutes listed, although time may vary across patients. Original procedures used and stimuli adapted for the purposes of this study. F - A/S, total number of words starting with F minus total number of words starting with A and S in alternation; score, total number of words generated in 60 seconds; Dy, dystonia; HVLT, Hopkins Verbal Learning Test; PD, Parkinson disease; RMT, Randt Memory Test.*
TABLE 2. Subject demographic and clinical characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age (years)</th>
<th>Age at onset (years)</th>
<th>Education (years)</th>
<th>Occupational level*</th>
<th>IQ (NART-R)</th>
<th>DRS score</th>
<th>Implantation side</th>
<th>Passes</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD1</td>
<td>M</td>
<td>72</td>
<td>61</td>
<td>14</td>
<td>6</td>
<td>103</td>
<td>131</td>
<td>Left</td>
<td>3</td>
</tr>
<tr>
<td>PD2</td>
<td>M</td>
<td>64</td>
<td>55</td>
<td>16</td>
<td>9</td>
<td>105</td>
<td>136</td>
<td>Left</td>
<td>3</td>
</tr>
<tr>
<td>PD3</td>
<td>M</td>
<td>65</td>
<td>55</td>
<td>20</td>
<td>9</td>
<td>111</td>
<td>142</td>
<td>Right</td>
<td>5</td>
</tr>
<tr>
<td>Dy1</td>
<td>F</td>
<td>32</td>
<td>27</td>
<td>15</td>
<td>7</td>
<td>115</td>
<td>144</td>
<td>Right</td>
<td>4</td>
</tr>
<tr>
<td>Dy2</td>
<td>F</td>
<td>31</td>
<td>10</td>
<td>14</td>
<td>6</td>
<td>116</td>
<td>137</td>
<td>Right</td>
<td>9</td>
</tr>
</tbody>
</table>

*Occupational level ranges from 1 through 9 (145).
PD, Parkinson disease; Dy, dystonia; M, male; F, female; Age, age at time of baseline testing; Age at onset, age at the time of disease onset; NART-R, National Adult Reading Test-Revised; DRS, Dementia Rating Scale; Passes, the number of recording/stimulating electrode passes during surgery.

Data Analysis

To standardize data across tasks, raw scores were converted to percentage of correct responses. On tasks with no upper limit (e.g., SCWT-Interference score), a percentile score was obtained from published norms. (Although another method for standardizing data would have been to calculate z scores for all measures, we administered some tasks using our own modifications [HVLT], and on other tasks, we did not use the standard outcome variable [RMT Picture Recognition]. Thus, because a z score could not be calculated for all measures, we used the percentage of correct responses method.) A cutoff score was used as a criterion for change rather than other statistical procedures because of the limited number of subjects and the large number of test scores. To use a criterion for change that was neither too strict for some tasks nor too liberal for others, >15% was selected (e.g., a 10% change on some tasks would equal a loss or gain of a single point, and this amount of change is not likely to be clinically relevant).

All patients were tested at baseline and after surgery in both the stimulation-off and stimulation-on conditions. Given the sample size, the preliminary nature of these data, and the large number of potential comparisons, we chose to focus on the overall cognitive effects of the DBS procedure by comparing patients’ test performance in the baseline condition with their performance in the stimulation-on condition (i.e., the “Procedure” comparison). For the Procedure comparison, Table 1 indicates which subjects changed by more than 15% on each task and if change occurred, in which direction it was. To evaluate whether there was a predominant direction of cognitive change (i.e., improvement or decline), when change occurred, a binomial comparison was performed for each patient. Only when the Procedure binomial comparison is significant are the follow-up “Surgery” (baseline to stimulation-off) and “Stimulation” (stimulation-on to stimulation-off) binomial comparisons interpreted. Table 3 indicates the number of tests that improved, declined, or did not change for each patient for the Procedure comparison. Although we could have performed binomial comparisons for all of the condition comparisons (i.e., Procedure, Surgery, Stimulation) for all subjects, this report is a preliminary analysis and its focus is more related to the feasibility of the PNIDBS; thus, we chose not to carry out a more extensive analysis at this time.

FEASIBILITY DATA

Parkinson Disease

For two of the three patients with PD (PD2 and PD3), the DBS procedure as a whole had a minimal effect on cognition. For these two patients, there was a 15% or less change in the Procedure comparison (baseline vs. stimulation-on) on most tests. When change was observed in PD2 and PD3, binomial comparisons revealed no significant difference between the number of neuropsychological test scores that improved versus the number that declined (see Table 3). PD Patient 1, however, declined on about one third of the test scores and improved on none. This Procedure binomial comparison was significant (p = 0.008). The decline for PD1 was observed in language (semantic and phonemic verbal fluency tasks), verbal memory (immediate and delayed cued recall trials of the HVLT and delayed free recall trial of the HVLT), and executive (SCWT-Interference score and the alternating fluency task) areas. The decline in fluency tasks is not likely due to oral motor slowing because this PD patient’s average ability to recite automatized sequences changed by only +1.3 seconds from the baseline to the stimulation-on condition.

Because the methodology of the PNIDBS calls for as-

<table>
<thead>
<tr>
<th>TABLE 3. Number of cognitive tests that improved (↑), declined (↓), or did not change (=) in the Procedure comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparison</td>
</tr>
<tr>
<td>-------------</td>
</tr>
<tr>
<td>Baseline versus stimulation-on</td>
</tr>
</tbody>
</table>
| PD, Parkinson disease; Dy, dystonia.
essment of patients in the stimulation-on and stimulation-off conditions, additional data were available to follow up this significant binomial comparison so as to try to identify the aspect of the procedure that was most associated with the cognitive change observed in PD1. By comparing the baseline scores with the stimulation-off condition scores (Surgery comparison), the cognitive effects of electrode placement could be examined. For the Surgery comparison, nine of PD1’s scores changed, with seven declining and two improving (Surgery binomial comparison: \( p = 0.090 \)). A separate comparison of the stimulation-off versus stimulation-on conditions (Stimulation comparison) permitted an evaluation of the cognitive effects of high-frequency stimulation. For the Stimulation comparison, seven of PD1’s scores changed, with five declining and two improving (Stimulation binomial comparison: \( p = 0.227 \)). The Surgery binomial comparison revealed a trend: performance on the semantic and phonemic verbal fluency tasks, BNT, SCWT-Interference score, immediate and delayed cued recall trials of the HVLT, and delayed recall trial of the short story declined, and performance on the Digit Span Backward task and number of semantic clusters improved.

On the depression measure, none of the patients with PD were depressed at baseline or at the time of the stimulation-on assessment.

Dystonia

Cognition in the two dystonia patients was minimally affected by the DBS procedure. When change did occur, there was no significant difference between the number of scores that improved versus the number that declined. In Dy2, however, there was some (\( p = 0.188 \)) cognitive improvement, with four scores on tests of attention (Digit Span Forward and BTA) and verbal recall (immediate and delayed HVLT cued recall) improving and one score on a test of visuospatial processing (ILOT) declining. On an exploratory basis, we inspected the Surgery and Stimulation comparisons for Dy2. For the Surgery comparison, three scores improved and none declined, and for the Stimulation comparison, two scores improved and three declined.

The mood of both dystonia patients improved after the DBS procedure. Dystonia Patient 1 was moderately depressed before surgery (baseline), and her mood improved to the mildly depressed range after the DBS procedure. A marked improvement in the mood of Dy2 occurred. At baseline, she scored in the severely depressed range, and after the DBS procedure, her GDS score was within normal limits.

DISCUSSION

Using this small sample of PD and dystonia patients, we have demonstrated the application and feasibility of the PNIDBS. The core neuropsychological test battery included in the PNIDBS was systematically developed, assesses a wide range of cognitive functions, can be completed by patients with severe motor disabilities, requires a relatively short time to administer, and has multiple forms for repeated administration. Although we recommend use of the PNIDBS core battery for standardized investigation of the cognitive effects of DBS for all these reasons, its relatively brief administration time (i.e., 1 hour) makes it particularly useful to investigators who may want to supplement it with additional tasks designed to explore particular cognitive functions in greater detail. Thus, investigators can both collect a standardized set of data across institutions and pursue more specific individualized questions in their own investigations of the cognitive effects of DBS. Because of these characteristics, the PNIDBS is also uniquely applicable for use in multicenter clinical trials.

Description of the Feasibility Data

Using the PNIDBS, the cognitive and affective effects of the DBS procedure were preliminarily evaluated in a small sample of movement disorder patients. For the most part, the DBS procedure with unilateral electrode placement in the STN or GPi seemed to have a minimal impact on the overall cognitive functioning of patients with movement disorders. This finding is similar to those reported by other groups who have examined cognitive functioning before and after either unilateral or bilateral STN or GPi stimulation in patients with PD (63,64,139); however, there are no results reported in dystonia patients to date. When change did occur in the present sample, cognitive functioning in most patients was not selectively improved or impaired by the procedure. One patient (PD1), however, did show a significant pattern of change wherein there was a decline on 32% of the measures and no change on the remaining measures. These reduced scores occurred on measures of verbal fluency, verbal recall, and executive functioning. Relative to the other patients with PD, PD1 was older at the time of disease onset and at the time of surgery; this patient had a lower education level and socioeconomic status (see Table 2). The mood of all three patients with PD remained relatively stable, with GDS scores falling within normal limits across the baseline and stimulation-on conditions.

Cognitive decline in a subset of patients after the DBS procedure has been reported elsewhere. Vingerhoets et al (139) observed that although there were no changes in cognitive functioning in their group of patients with PD as a whole (n = 20) after GPi DBS, a subset of 8 patients was cognitively impaired after the surgery. This subset of postoperatively impaired patients was significantly older and had received higher doses of levodopa before surgery, presumably indicating that they were more se-
verely affected by their disease. The present findings and those of Vingerhoets et al (139) may indicate that there are specific patient characteristics that are risk factors for cognitive decline after DBS surgery. In fact, several of the demographic variables that differed between the postoperatively impaired and intact patients in the present study and in the report by Vingerhoets et al (139) (e.g., older age, lower education level, or lower socioeconomic status) have previously been found to be associated with a higher risk for cognitive impairment after brain injury (140–142).

The PNIDBS employs a design that allowed for further investigation of which aspect of the procedure (Surgery or Stimulation) was associated with cognitive change, when change did occur. PD Patient 1 demonstrated a substantive difference in the number of scores that declined versus the number that improved in the Surgery comparison but not in the Stimulation comparison. Thus, the aspect of the procedure that seemed to be most closely associated with the cognitive decline observed in this patient was electrode placement. For the DBS procedure, to achieve optimum targeting of the stimulation electrode, several passes of a recording probe through the brain may be required. With implantation in the STN, for each of the targeting attempts, the probe is passed through the prefrontal cortex as it is moved through the brain to the STN. The areas of cognitive impairment (i.e., verbal fluency, verbal memory, executive function) in PD1 after the procedure are consistent with the side of surgery (left) as well as with the cognitive areas that would be expected to change after manipulation of subcortical-prefrontal circuits.

In contrast to the decline that occurred in PD1, some cognitive improvement was observed in Dy2. This improvement was characterized by higher scores on tests of attention and verbal memory. Interestingly, the baseline severe depression in Dy2 remitted after the DBS procedure. It is possible that the more mild cognitive improvement observed in this patient is a function of improved mood. This tentative conclusion is supported by the specific type of cognitive function that improved after the procedure. It has been reported that depression can adversely affect attention and memory (110) and that improvement in these cognitive domains typically occurs when the depression remits (143). Cognition in Dy1 was minimally affected, with no trend toward select improvement or decline. Her mood improved slightly from the moderately to mildly depressed range after surgery.

**PNIDBS**

As demonstrated in this report, the methodology proposed in the PNIDBS is realistically feasible to execute. In describing the neuropsychological findings in this small sample of movement disorder patients, we have also shown that data collected with the PNIDBS are similar to those described in earlier reports and that this neuropsychological program can answer more specific questions about the cognitive changes that may occur after the DBS procedure relative to methods employed in other studies. The primary clinical question of interest in this area of research concerns the overall cognitive effects of the DBS procedure. As demonstrated here and in other studies, most patients tolerate it well; however, there are individuals who might benefit motorically from the procedure but may be left with reduced areas of cognitive functioning after surgery. Careful investigation of patient characteristics in relation to neuropsychological changes after the DBS procedure can provide information about which candidates are likely to tolerate the procedure well from a neuropsychological perspective. Our results suggest that the presence of several demographic and/or clinical risk factors may differentiate between patients who are likely to develop significant postoperative cognitive impairment and those who are not. Information about which risk factors and how many factors must be present for significant cognitive decline to occur would help physicians and patients evaluate the overall benefits and risks of the procedure as they pertain to an individual patient.

There are also more basic research-oriented questions that can be addressed using the methodology described in the PNIDBS. The DBS procedure offers a unique opportunity to study cognition in human subjects before, during, and after a largely reversible brain manipulation. Unlike direct cortical stimulation or the Wada procedure, the time available for investigating different aspects of cognitive functioning in each condition is not limited to a few seconds or minutes. Comprehensive neuropsychological assessment of patients in both the stimulation-on and stimulation-off conditions is possible and can be used to achieve a better understanding of which aspects of the DBS procedure cause changes in cognitive functioning, if change does occur. Testing in these two postoperative conditions can also be used to further delineate how selected areas of cognitive functioning are affected by manipulation of subcortical-prefrontal neuroanatomic circuits.

Thus, the methodology of the PNIDBS not only addresses clinical questions regarding the overall cognitive effects of the DBS procedure but also investigates more basic scientific questions about how different types of brain manipulations (e.g., electrode placement or high-frequency stimulation) in specific brain areas (e.g., STN, GPi, VIM) affect higher order cognitive functioning. Preliminary data presented here and elsewhere (65–67) give some indication that the two aspects of the DBS procedure might have differential effects on select areas of cognitive functioning in some patients.
Future Directions

Our presentation of methodological issues in evaluating the neuropsychological effects of the DBS procedure, although extensive, is by no means all-inclusive. It does, however, serve the purpose of proposing a set of tasks and a model of assessment that others can discuss, for example, in the context of a multicenter consensus meeting. As research in this area progresses, a clearer understanding can be obtained of how manipulation of subcortical-prefrontal circuits via the DBS procedure affects specific cognitive areas. Study of additional subjects will also help to elucidate which patients are susceptible to either positive or negative change after the DBS procedure. For example, it will be interesting to observe if unique patterns of cognitive change emerge among those with left, right, or bilateral implantation; those in different populations of movement disorder patients (e.g., PD, ET, dystonia); or those in subgroups within a population (e.g., younger versus older patients with PD) after the DBS procedure. Although the current sample was too small to address all these issues, we are continuing to collect data using the PNIDBS in an effort to follow up these avenues of investigation. We have also initiated projects to collect normative data for the measures included in the PNIDBS in various types of movement disorder patients as well as in normal controls.

Acknowledgments: This research was supported in part by NIMH grant 1F31MH11809-01A1 (C.E.M.), US Food and Drug Administration grant FD-001452 (M.F.B., C.W.O, I.M.G., and D.J.W.), the Bachmann Strauss Dystonia and Parkinson's Foundation (M.F.B., C.W.O., I.M.G., and D.J.W.), NIMH grant MH42172 (J.C.B.), and the Mount Sinai Medical Center General Clinical Research Center grant PHS M01-RR00071 (M.F.B. and C.W.O.).


The authors thank Martin Sliwinski for his comments.

REFERENCES

DEEP BRAIN STIMULATION


76. Beatty WW, Monson N, Goodkin DE. Access to semantic memory


